Remarks

I. Addressing the Examiner's Rejection of Claims 6, 7, 11, 15, 17, and 18 Under 35 U.S.C. §102(e).

The Examiner rejected claims 6, 7, 11, 15, 17, and 18 under 35 U.S.C. §102(e) asserting that the claims are anticipated by Bischoff, et al., U.S. Patent No. 6,080,578.

In the present application, independent claims 11 and 15 are pending. Following herein below, the applicants set forth their arguments that the cited reference does not anticipate the claimed invention at least with respect to the limitations present in the independent claims. Accordingly, the dependent claims define over the cited prior art at least by virtue of their inclusion of the limitations of the independent claims.

Applicants submit that the reference of Bischoff, et al., does not anticipate the claimed invention for reasons of record as previously discussed by applicants; specifically, (1) the reference of Bischoff, et al, does not teach all of the elements of the present invention; and (2) the Examiner has failed to establish a *prima facie* case of inherency as the reference of Bischoff, et al, does not inherently teach all of the elements of the present invention.

Finally, applicants briefly discuss how the fact pattern of the present case distinguishes it from the fact patterns of the case law cited by the Examiner.

1. The reference of Bischoff, et al, does not expressly teach all of the elements of the present invention.

Federal Circuit decisions repeatedly emphasize that anticipation can be established only if all the elements of a claimed invention are identically set forth in a single prior art reference. The test is strict, not substantial, identity. *See, e.g., Transclean Corp. v. Bridgewood Services, Inc.*, 290 F.3d 1364, 62 USPQ2d 1865 (Fed. Cir. 2002); *Sandt Technology, Ltd. V. Resco Metal and Plastics Corp.*, 264 F.3d 1344, 60 USPQ2d 1091 (Fed. Cir. 2001); *EMI Group North America Inc. v. Cypress Semiconductor Corp.*, 268 F.3d 1342, 1350, 60 USPQ2d 1423 (Fed. Cir. 2001) ("A prior art reference anticipates a patent claim if the reference discloses, either expressly or inherently, all of the limitations of the claim").

Both of the pending independent method claims (i.e., claims 11 and 15) comprise two limitations not taught by the reference of Bischoff, et al., (i) a limitation relating to preferential killing of dividing endothelial cells compared to quiescent endothelial cells, and (ii) a limitation that the claimed method is carried out by direct administration of a

replication competent adenovirus, comprising a mutation in an E1A CR2 RB family member binding region, to endothelial cells. Further, claim 11 contains the limitation that the mutant adenovirus (i.e., a replication competent adenovirus comprising a mutation in an E1A CR2 RB family member binding region) versus wild-type adenovirus replicates to higher titers in the dividing endothelial cells, and claim 15 contains the limitation of "controlling angiogenesis in an animal." The reference of Bischoff, et al., does not teach either of these limitations. Claims 11 and 15 are as follows:

> 11. In a cell population comprising dividing and quiescent endothelial cells, a method for killing said dividing endothelial cells with substantially less killing of said quiescent endothelial cells, said method comprising contacting said cell population under infective conditions with a replication competent adenovirus, said adenovirus comprising a mutation in an E1A CR2 RB family member binding region of said adenovirus, and allowing sufficient time for said mutant adenovirus to infect said cell population, wherein said mutant adenovirus replicates to higher titers in said dividing cells than wild type adenovirus and said contacting is by direct administration of the replication competent adenovirus to the cell population.
>
> 15. A method for controlling angiogenesis in an animal by substantially and selectively killing dividing microvascular endothelial cells compared to quiescent microvascular endothelial cells, said method comprising administering to said animal in need of said control a replication competent adenovirus comprising a mutation in an E1A-CR2 RB family member binding region of said adenovirus, and allowing sufficient time for said mutant adenovirus to infect said microvascular endothelial cells, wherein said administering is by direct administration of the replication competent adenovirus to the microvascular endothelial cells.

The teachings of the reference of Bischoff, et al., relate to "methods and compositions for **ablating neoplastic cells by infecting the neoplastic cells** with a recombinant adenovirus which is substantially replication deficient in non-neoplastic cells and which exhibits at least a partial replication phenotype in neoplastic cells" (*see* Bischoff, et al., col. 3, lines 8-13; emphasis added). The reference of Bischoff, et al., teaches "(t)he mutant virus is able to substantially produce a replication phenotype in **neoplastic cells** but is substantially unable to produce a replication phenotype in non-replicating, non-neoplastic cells having essentially normal p53 and/or RB function" (*see* Abstract of Bischoff, et al.; emphasis added).

The reference of Bischoff, et al., does not teach that replication competent

adenovirus, comprising a mutation in an E1A CR2 RB family member binding region, demonstrates enhanced replication in and killing of dividing endothelial cells (*e.g.*, microvascular endothelial cells) versus quiescent endothelial cells.

Also, the reference does not teach direct administration of a mutant adenovirus to endothelial cells. Further, the reference of Bischoff, et al., provides no teaching concerning mutant adenovirus replicating to higher titers in the dividing endothelial cells than wild type adenovirus as is set forth as a limitation in claim 11. Finally, the reference of Bischoff, et al., does not teach control of angiogenesis in an animal as a method of controlling neoplastic cell growth.

Accordingly, applicants submit that the reference of Bischoff, et al., does not teach all of the elements of the claimed invention. Therefore, in order to assert that the reference anticipates the presently claimed invention, the Examiner must establish that the reference inherently teaches all of the claimed elements of the methods of the present invention.

2. The Examiner has failed to establish a *prima facie* case of inherency.

First, inherency is not present when prior art is only capable of being modified. To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *See Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991); emphasis added. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *See Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (C.C.P.A. 1981)). The fact that a prior art reference is capable of being modified and the resulting modification would anticipate the invention is not sufficient to support anticipation based on inherency. In *In re Robertson* (169 F.3d 743, 749 USPQ2d 1949 (Fed. Cir. 1999)), the Federal Circuit reversed an anticipation holding because the prior art was only capable of being modified and one of ordinary skill would not have recognized such modification.

In the present application, a method of killing dividing endothelial cells with substantially less killing of quiescent cells by contacting the cells under infective conditions with a mutant adenovirus is not inherent in the teachings of Bischoff, et al., for the following

reasons. Not all tumors comprise neoplastic cells that are $RB^{(-)}$ (*see* Bischoff, et al., col. 7, lines 47-63; col. 9, lines 20-55). The reference of Bischoff, et al., teaches method of ablating tumor cells by administration of a mutant adenovirus comprising a mutation in the E1A CR2 domain to:

> A cell population (such as a mixed cell culture or a human cancer patient) which comprises a subpopulation of neoplastic cells lacking RB function and a subpopulation of non-neoplastic cells which express essentially normal RB function can be contacted under infective conditions (i.e., conditions suitable for adenoviral infection of the cell population, typically physiological conditions) with a composition comprising an infectious dosage of a E1a - $RB^{(-)}$ replication deficient adenovirus. Such contacting results in infection of the cell population with the E1a -$RB^{(-)}$ replication deficient adenovirus. The infection produces preferential expression of a replication phenotype in a significant fraction of the cells comprising the subpopulation of neoplastic cells lacking RB function but does not produce a substantial expression of a replicative phenotype in the subpopulation of non-neoplastic cells having essentially normal RB function. The expression of a replication phenotype in an infected $RB^{(-)}$ cell results in the death of the cell, such as by cytopathic effect (CPE), cell lysis, apoptosis, and the like, resulting in a selective ablation of neoplastic $RB^{(-)}$ cells from the cell population. (Bischoff, et al., col. 9, line 56, to col. 10, line 9; emphasis added.)

The Examiner asserts the following:

> It is noted that patients comprising tumors comprise both dividing cells, such as proliferating cancer cells and proliferating microvascular endothelial cells associated with the tumor, as well as non-dividing non-cancerous cells. For instance, tumors are highly vascularized with blood vessels which are comprised of dividing and non-dividing endothelial cells. Directly administering an adenoviral vector to a tumor would result in administration of the vector to the blood vessels of the tumor. Therefore, administering the vector taught by Bischoff to a subject having a tumor would necessarily result in substantially and selectively killing dividing endothelial cells (including dividing microvasculature) and cancer cells in the subject. (*See* Office action, mailed 16 June 2008, page 4.)

However, the reference of Bischoff, et al., only teaches the use of E1A-$RB^{(-)}$ replication defective adenovirus mutants in methods of ablating $RB^{(-)}$ neoplastic cells. It is not inherent in the method taught by Bischoff, et al., to infect endothelial cells with E1A-$RB^{(-)}$ replication defective adenovirus mutants regardless of the RB-expression status of the neoplastic cells, as in the presently claimed method. Even in the situation where a tumor does not display loss of RB gene function, the method of the present invention is effective to kill dividing

endothelial cells within the tumor.

Following the teachings of the reference of Bischoff, et al., there is no reason that one of ordinary skill in the art would administer an adenovirus comprising a mutation in an E1A CR2 RB family member binding region to a tumor cell population that did not comprise $RB^{(-)}$ cells. However, following the methods of the claimed invention one of ordinary skill is directed to treat populations of cells comprising tumor cells and dividing endothelial cells with an adenovirus comprising a mutation in an E1A CR2 RB family member binding region regardless of the RB-expression status of the target tumor.

Accordingly, the mere fact that a one of ordinary skill in the art may administer an adenovirus comprising a mutation in an E1A CR2 RB family member binding region to a tumor cell population comprising $RB^{(-)}$ cells does not make it certain that one of ordinary skill in the art would do the same for any tumor cell populations (*e.g.*, when the tumor cell population is not $RB^{(-)}$). As noted above, inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *See Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (C.C.P.A. 1981)).

Further, in regard to claim 11, there is no reason for one of ordinary skill in the art to conclude from the teachings of the reference of Bischoff, et al., that administration of the mutant adenovirus to dividing endothelial cells results in the mutant adenovirus replicating to higher titers in the dividing cells than wild type adenovirus regardless of the RB-expression status of associated tumor cells. Also, in regard to claim 15, there is no reason for one of ordinary skill in the art to conclude from the teachings of the reference of Bischoff, et al., that direct administration of the replication competent adenovirus to dividing microvascular endothelial cells would provide a method for controlling angiogenesis in an animal regardless of the RB-expression status of the tumor cells.

Accordingly, even if, *in arguendo,* the reference of Bischoff, et al., is capable of being modified to achieve the method of the present invention, the Examiner has not presented any evidence that makes it clear that the missing descriptive matter described herein above is necessarily present in the cited reference.

Second, "[a] reference includes an inherent characteristic if that characteristic is the

'natural result' flowing from the reference's explicitly explicated limitations." *See Eli Lilly & Co. v. Barr Laboratories, Inc.*, 251 F.3d 955, 970, 58 USPQ2d 1865 (Fed. Cir. 2001). In the present case, the claimed invention is not a natural result flowing from the disclosure of the Bischoff, et al. The reference of Bischoff, et al., lacks descriptive matter related to killing of dividing endothelial cells by direct administration of a mutant adenovirus.

In the absence of the teachings of the present specification, one of ordinary skill in the art would not be guided to use replication competent adenovirus to preferentially kill dividing endothelial cells relative to killing of quiescent endothelial cells, which in and of itself provides an art recognized cancer treatment (i.e., disruption of tumor angiogenesis) distinct from direct killing of tumor cells (i.e., neoplastic cells). The claimed methods of the present invention relate to direct administration of mutant adenovirus to dividing endothelial cells to provide preferential killing of dividing endothelial cells relative to killing of quiescent endothelial cells, notably microvascular endothelial cells, by the mutant adenovirus.

The endothelium comprises a single layer of flat cells that line the interior surface of blood vessels. The endothelium forms an interface between circulating blood in the lumen and the rest of the vessel wall. Endothelial cells are the cells that make up the inside of blood vessels. Angiogenesis is the formation of new blood vessels. Angiogenesis has come to be appreciated as a continuous and important process in tumor development, wherein a tumor may gain an independent blood supply. The process of angiogenesis is believed to be driven by the tumor releasing signals that induce angiogenesis, such as VEGF, by binding to endothelial cell receptors near the tumor (*see, e.g.*, Berse, B., et al., Molec. Cell. Biol. 1992 Feb;3(2):211-20); Warren, R.S., et al., J. Clin. Invest. 1995 Apr;95(4):1789-97; both references are of record in the present application). The control of tumor angiogenesis is generally seen to be an alternative method of controlling tumor growth versus direct destruction of tumor cells (*see, e.g.*, Berse, et al., paragraph bridging pages 218-219; Warren, et al., paragraph bridging cols. 1-2, page 1789). Accordingly, the claimed invention is not a natural result flowing from the disclosure of the Bischoff, et al., reference because the reference teaches "methods and compositions for **ablating neoplastic cells by infecting the neoplastic cells** with a recombinant adenovirus which is substantially replication deficient in non-neoplastic cells and which exhibits at least a partial replication phenotype in neoplastic

cells" (*see* Bischoff, et al., col. 3, lines 8-13; emphasis added)..

The reference of Bischoff, et al., does not contain any explicitly explicated limitations from which the 'natural result' flowing from the reference's teachings would result in the use of the described adenoviral vectors as an alternative method of controlling tumor growth, that is, direct administration of mutant adenovirus to endothelial cells for preferential killing of dividing endothelial cells relative to killing of quiescent endothelial cells, notably microvascular endothelial cells. The reference of Bischoff, et al., teaches only the killing of $RB^{(-)}$ tumor cells by administration of replication competent adenovirus comprising a mutation in an E1A CR2 RB family member binding region to the $RB^{(-)}$ tumor cells.

There is no teaching in the reference of Bischoff, et al., that would guide one of ordinary skill in the art to use the methods of the present invention to achieve a method for preferential killing of dividing endothelial cells relative to killing of quiescent endothelial cells. For example, in a situation where a target tumor (regardless of RB-expression status of the tumor cells) did not respond to direct killing of neoplastic cells by a selected method (*e.g.*, chemotherapy), in view of the teachings of the present specification one of ordinary skill in the art may choose to administer a mutant adenovirus to the dividing endothelial cells to reduce or eliminate angiogenesis which provides a blood supply to a tumor. The teachings of Bischoff, et al., would not direct one of ordinary skill in the art to such an approach. Inherency must flow as a necessary conclusion from the prior art, not simply a possible one. *See, e.g., In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (C.C.P.A. 1981). Accordingly, the teachings of the reference of Bischoff, et al., do not inherently anticipate the methods of the claimed invention.

Third, the Federal Circuit has cautioned that all claimed elements must be found in the prior art for anticipation to be found:

> For a prior art reference to anticipate a claim, the reference must disclose each and every element of the claim with sufficient clarity to prove its existence in the prior art .... Although this disclosure requirement presupposes the knowledge of one skilled in the art of the claimed invention, that presumed knowledge does not grant a license to read into the prior art reference teachings that are not there. *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1473, 43 USPQ2d 1481, 1490 (Fed. Cir. 1997).

In the present case, the Examiner has presupposed the knowledge of one skilled in the art (i.e., "patients comprising tumors comprise both dividing cells, such as proliferating

cancer cells and proliferating microvascular endothelial cells associated with the tumor," *see* Office action, mailed 16 June 2008, page 4); however, that presumed knowledge does NOT grant the Examiner a license to read into the reference of Bischoff, et al., teachings that are not there (*e.g.*, a method of killing dividing endothelial cells with substantially less killing of quiescent cells by direct administration of a mutant adenovirus to the cells under infective conditions). Further, the presupposed knowledge applied by the Examiner does not prove the existence in the cited prior art of a method of administering a replication competent adenovirus comprising a mutation in an E1A CR2 RB family member binding region to tumor cells regardless of RB-expression status. The reference of Bischoff, et al., does not teach or suggest any such method.

In view of the above-presented arguments, applicants submit that the Examiner has failed to establish a case of anticipation for the claimed invention. Further, the Examiner has failed to establish a *prima facie* case of inherency.

3. Brief discussion of the case law cited by the Examiner.

In the Office action, mailed 16 June 2008, the Examiner recites several cases to support the asserted inherency rejection. Following herein, applicants summarize important distinctions between the fact patterns of the cases recited by the Examiner and the present application.

First, regarding *In re Best* the Examiner asserts the following:

> Applicant is reminded that MPEP § 2112.01 indicates, "[T]he claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPO 430,433 (CCPA 1977)." (*See* Office action, mailed 16 June 2008, page 4.)

The holding regarding inherency in *In re Best* was discussed by the CCPA as follows:

> All the positive process limitations are expressly disclosed except for the functionally expressed rate of cooling. However, there is nothing to indicate that this rate of cooling in any way differs from the normal rate resulting from removal of the heat source. Thus, the examiner's conclusion that those parameters of the resultant product which are recited in the appealed claims but are not expressly disclosed in the reference would be inherent is a reasonable one, absent convincing evidence to the contrary. (*In re Best*, 562 F.2d 1252, 1254, 195 USPO 430, 433 (CCPA 1977); emphasis added.)

In the present case the prior art method is not substantially identical to the presently

claimed method. First, the presently claimed "positive process limitations" are not disclosed by the reference of Bischoff, et al. The reference teaches "methods and compositions for **ablating neoplastic cells by infecting the neoplastic cells with a recombinant adenovirus** which is substantially replication deficient in non-neoplastic cells and which exhibits at least a partial replication phenotype in neoplastic cells" (*see* Bischoff, et al., col. 3, lines 8-13; emphasis added). The present invention claims preferential killing of dividing endothelial cells compared to quiescent endothelial cells carried out by direct administration of a mutant adenovirus to endothelial cells. Second, the method of the present invention does in fact differ from the method taught by the reference of Bischoff, et al. For the reasons discussed herein above, the method of direct ablation of neoplastic cells comprising administration of a mutant adenovirus to the neoplastic cells taught by the reference is different from the presently a method of killing dividing endothelial cells by direct administration of mutant adenovirus; specifically, these methods relate to different approaches for the treatment of tumors (direct ablation of tumor cells versus targeting angiogenesis, respectively), wherein the methods of the present invention, unlike the teachings of the reference, are not limited to tumor cells that have lost RB gene function.

Second, regarding *Schering Corp. v. Geneva Pharm. Inc.*, the Examiner asserts the following:

> There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). (*See* Office action, mailed 16 June 2008, page 4.)

The holding regarding inherency in *Schering Corp. v. Geneva Pharm. Inc.* was discussed by the Federal Circuit as follows:

> Other precedents of this court have held that inherent anticipation does not require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure. *E.g., In re Cruciferous Sprout Litig., 301 F.3d 1343, 1351 (Fed. Cir. 2002)*; *Mehl/Biophile Int'l Corp. v. Milgraum, 192 F.3d 1362, 1366 (Fed. Cir. 1999)* ("Where . . . the result is a necessary consequence of what was deliberately intended, it is of no import that the article's authors did not appreciate the results."). *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); emphasis added.

As discussed herein above, the result of the method of the present invention is not a

necessary consequence of what was deliberately intended by the teachings of the reference of Bischoff, et al.. This is certainly the case in view of the fact that the reference only teaches administration of E1A-RB$^{(-)}$ adenovirus mutants for ablation of tumor cells that have lost RB gene function. As discussed herein above, there is no inherent disclosure of the method of the present invention in the reference of Bischoff, et al.

Third, regarding the Examiner's point citations of *In re Spada* and *In re Ludtke,* the citations provided by the Examiner relate to the anticipation of products; however, the pending, rejected claims are directed to methods not products. Accordingly, the Examiner's reliance on these cases is inappropriate.

Finally, the Examiner attempts to shift the burden of proof for lack of anticipation to the applicants (citing "*In re Best, Bolton, and Shaw,* 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown,* 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972)" *see* Office action, mailed 16 June 2008, page 5). As discussed herein above, the Examiner has failed to establish a case for anticipation. Accordingly, further evidence from applicants is not required. Further, this point citation is also related to prior art products and not methods.

4. Summary.

For the foregoing reasons, applicants respectfully submit that the Examiner has erred in rejecting claims 6, 7, 11, 15, 17 and 18 of this application. Specifically, the reference of Bischoff, et al, does not expressly or inherently teach all of the claimed elements of methods of the present invention, for example, as follows:

- The reference does not teach endothelial cells.
- The reference does not teach direct administration of a replication competent adenovirus, comprising a mutation in an E1A CR2 RB family member binding region, to endothelial cells.
- The reference does not teach preferential killing of dividing endothelial cells compared to quiescent endothelial cells by administration of such mutant adenovirus.
- The reference teaches only methods for specifically ablating RB$^{(-)}$ tumor cells by infecting RB$^{(-)}$ tumor cell populations with a E1A-RB$^{(-)}$ replication defective adenovirus mutants; that is, the reference does not teach

administration of such mutant adenovirus for preferential killing of dividing endothelial cells in cell populations without regard to RB-expression status of the cells in the population.

- The reference does not teach that such mutant adenovirus replicates to higher titers in the dividing endothelial cells versus wild-type adenovirus.
- The reference does not teach controlling angiogenesis in an animal by infection of dividing endothelial cells with such mutant adenovirus.

Accordingly, in view of the above-presented arguments, applicants submit that the Examiner has failed to establish a case of anticipation for the claimed invention. Further, the Examiner has failed to establish a *prima facie* case of inherency. Applicants therefore respectfully request withdrawal of the rejection of the claims asserted under 35 U.S.C. §102(e).

II. Addressing the Examiner's Rejections of Claims 26 and 27 Under 35 U.S.C. 103(a).

The Examiner rejected claim 26 under 35 U.S.C. 103(a) asserting that the claim is unpatentable over Whyte, et al., J. Virol. 1988, in view of Bischoff, et al., U.S. Patent No. 6,080,578.

The Examiner rejected claim 27 under 35 U.S.C. 103(a) asserting that the claim is unpatentable over Jelsma, et al., Virol. 1989, in view of Bischoff, et al., U.S. Patent No. 6,080,578.

In this paper, applicants cancel claims 26 and 27. Cancellation of claims 26 and 27 obviates the rejection of these claims.

III. Addressing the Examiner's Objection to Claims 8-10, 19, 20, and 34.

The Examiner indicated claims 8-10, 19, 20, and 34 are objected to as being dependent upon a rejected base claim but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

In view of the above-presented arguments, applicants submit that the presently claimed invention is not anticipated by the prior art. Accordingly, applicants respectfully request withdrawal of the objection to the claims.

IV. Conclusion.

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please direct all further communications in this application to:

Gregory Giotta, Ph.D., Esq.
(Reg. No. 32,028)
ONYX Pharmaceuticals, Inc.
2100 Powell Street
Emeryville, CA 94608
Phone: (510) 597-6502
Facsimile: (510) 597-6610.

If the Examiner notes any further matters that the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact Gregory Giotta at (510) 597-6502 or the undersigned at (650) 780-9030.

Respectfully submitted,

Date: 16 Dec 2008 By: Gary R Fabian

Gary R. Fabian, Ph.D.
Registration No. 33,875
Agent for Applicants